IV. REMARKS

Claims 1-9 are pending in this application. Claims 2, 5, and 6 are withdrawn. By this Amendment, the Abstract, specification, and claim 4 are amended. The amendments are supported by the specification and the claims as originally filed. In particular, the Abstract, specification, and claim 4 are amended to correct minor informalities and to comply with U.S. patent practice, as requested by the Examiner. The specification was also amended to include the amendments to the specification in the Preliminary Amendment filed October 8, 2004. A clean version and a marked-up version of the substitute specification are attached for the Examiner's convenience. No new matter is added.

Applicants respectfully request acknowledgement of the citation to DE4420523 in the Information Disclosure Statement filed October 8, 2004. For the Examiner's consideration, Applicants enclose a partial translation of the abstract from esp@cenet.com. Applicants also enclose a second copy of DE4420523 for the Examiner's convenience.

The specification and abstract are objected for asserted informalities. Applicants respectfully submit that that these objections are overcome by the above amendments to the specification and abstract. Accordingly, Applicants respectfully request withdrawal of the objections to the specification and abstract.

Claim 4 is objected to for asserted indefinite formatting. Applicants respectfully submit that this objection is overcome by the above amendments to claim 4. Accordingly, Applicants respectfully request withdrawal of the objection to claim 4.

Claims 1, 3, 4, and 7-9 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. This rejection is traversed.

Applicants agree with the Examiner that the specification is "enabling for reducing the degenerative effects on cartilaginoid matrix" (Office Action, page 4).

However, Applicants also submit that the specification provides sufficient support to enable preventing degenerative effects on cartilaginoid matrix (claims 1, 3, 4, and 7-9) and preventing relapses of degenerative effects on cartilaginoid matrix (claim 9).

As stated on pages 28-29 of the specification, the progression of arthritic disease is due to the imbalance between pro-inflammatory mediators (e.g., IL-6 and TNF-α) and anti-inflammatory mediators (e.g., TGF-β). The compounds of the presently claimed invention are effective in reducing or eliminating the imbalance of these mediators by increasing the formation of anti-inflammatory mediators and decreasing the formation of pro-inflammatory mediators. Examples F2, F3, and F5 in the specification show that the pro-inflammatory mediators (IL-6 and TNF-α) are decreased or suppressed while Examples F1, F4, and F6 show that the anti-inflammatory mediators (TGF-β) are increased. As such, administration of the compounds of the presently claimed invention reduces or eliminates the imbalance between the anti-inflammatory and the pro-inflammatory mediators, and thereby prevents the degeneration of the cartilaginoid matrix. Thus, Applicants submit that the specification provides sufficient support for the prevention of degeneration of the cartilaginoid matrix as in present claims 1, 3, 4, and 7-8 and prevention of relapses of degenerative effects on cartilaginoid matrix as in present claim 9, and no undue experimentation is required.

Accordingly, for at least the above reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 3, 4, and 7-9 under 35 U.S.C. § 112, first paragraph, for lack of enablement.

Claims 1, 3, 4, and 7-8 are rejected under 35 U.S.C. § 102(b) as being anticipated by Armour et al. ("Inhibition of bone resorption in vitro and prevention of ovariectomy-induced bone loss in vivo by flurbiprofen nitroxybutylester (HCT 1026),"Arthritis and Rheumatism, 44(9):2185-2192 (Sept. 2001)).

Present claim 1 discloses "[a] method of preventing or reducing the degenerative effects on cartilaginoid matrix comprising administering to a subject with arthritis an effective amount of one or more compounds or salts thereof having the following formula: A-$(B)_{b0}$-$(C)_{c0}$-$N(O)_S$ (I)" (emphasis added). Applicants respectfully submit that Armour et al. does not disclose the method of present claim 1. In contrast, Armour et al. merely discloses *in vivo* administration of HCT1026 (flurbiprofen nitroxybutylester) to a mouse model of ovariectomy-induced bone loss and that it inhibited interleukin-1-induced bone resorption and osteoclast formation (Armour et al., page 2185, Abstract).

Applicants respectfully submit that the phrase "degenerative effects on cartilaginoid matrix" in present claim 1 does not include bone loss in a joint due to bone resorption or osteoclast formation. Cartilaginoid matrix relates to cartilage (see, e.g., the first full paragraph on page 30 of the specification, disclosing "reducing ... cartilage degeneration process in arthritic disease"), a type of connective tissue generally found in the joints and around bones. In contrast, bone resorption is described as the process by which osteoclasts break down bone and release the minerals, resulting in a transfer

of calcium from bone fluid to the blood. As such, Armour et al. merely discloses the effect of HCT1026 on osteoclast cells in bones, and does not disclose any effect of HCT1026 on chondrocytes (the cells found in cartilage), much less reducing the degenerative effects on cartilaginoid matrix as in the method of the presently claimed invention.

As Armour et al. does not disclose each element of the presently claimed invention, Applicants respectfully submit that Armour et al. does not anticipate the presently claimed invention. Accordingly, for at least the above reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 3, 4, and 7-8 under 35 U.S.C. § 102(b) as being anticipated by Armour et al.

V. CONCLUSION

Applicants respectfully submit that this application is in condition for allowance and such action is earnestly solicited. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below to schedule a personal or telephone interview to discuss any remaining issues.

In the event this paper is not considered to be timely filed, Applicant hereby petitions for an appropriate extension of time. The fee for this extension may be charged to our Deposit Account No. 01-2300, referring to Attorney Docket No. **026220-00055**. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 01-2300, referencing Attorney Docket No. **026220-00055**.

Respectfully submitted,

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Enclosures: Substitute Specification (clean and marked-up versions)
English Abstract of DE4420523
DE4420523